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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,976	12/05/2005	Seetharama A. Acharya	96700/1023	6788

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,976	ACHARYA ET AL.	
	Examiner	Art Unit	
	Samuel W. Liu	1656	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/14/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

Claims 1-27 are pending.

The preliminary amendment filed 7/20/06 which amends claims 17-19 and 22 has been entered. Claims 1-27 are examined in this Office action.

Continuation data and priority

This application is a 371 application of PCT/US03/40407 filed 12/18/2003. Applicant's claim for the benefit of a prior-filed application 60436149 filed 12/23/2002 under 35 U.S.C. 119(e) is acknowledged.

IDS

The references cited in the IDS filed 6/14/05 have been considered by Examiner.

Objections to specification

The disclosure is objected to because of the following informalities:

(1) The continuing data of the instant application should be updated.

(2) At paragraph [0005], line 5, "PEGylated" should be spelled out for the first instance of use.

Objections to claims

Claims 1-27 are objected because in claim 1, "PEG" should be spelled in full for the first time recitation in the claims.

Objections to drawings

The drawings filed 6/14/05 are objected to because in Figure 2A, the vertical axis lack the unit for "Absorbance"; and in Figure 3, the horizontal axis lacks index for "ml";

and because the labeling of "Figure 8" is unclear, and the legend (description) of Figure 8 should no presented in the drawing per se.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 7 and 19-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7 and 19-21 recites "non-hypertensive"; the recitation is not apparent whether or not it refers to the a state of hypertension condition caused by the interaction of Hb with O_2 or/and a state of oxygen tension associated with the Hb molecule thereof.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application

being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

• Claims 1-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Winslow et al. (US 6974795 B2).

In Examples 2-3, Winslow et al. teach a polyethylene glycol modified (PEGylated) hemoglobin (Hb), i.e., Mal-PEG-Hb, which is produced by introducing additional thiol groups by iminothiolation; the number of reactive thiol groups thus increase from 2 to 6 (col. 17, lines 40-45); thus, there are 6 PEG chains conjugated to Hb through said thiol groups. Therefore, Winslow et al. the product of claim 1.

*Note that Hb has tow intrinsic Cys-93(β) residues.

Winslow et al. teach that the PEG has molecular weight (MW) of 5,000 daltons, which anticipates claims 2-3.

Winslow et al. teach that conjugating Mal-PEG to Hb via succinimidyl linkage (col. 12, lines 30-32), which anticipates claims 4-5.

Since the PEGylated Hb taught by Winslow has the same structural characteristics as that of the instant claims, and since a chemical composition and its properties are inseparable, non-hypertensive is an inherent property of the PEGylated Hb. Therefore, Winslow et al. also teach claim 7.

At Examples 2-3, Winslow et al. teach a method of the PEGylated Hb comprising step 1 (thiolation): reacting iminothiolane with Hb protein; this introduce free thiol groups into Hb (see col. 16, lines 6-7), and step 2 (PEGylation of thiolated Hb): reacting

the thiolated Hb with Mal-PEG wherein "Mal" is maleimidyl group (patent claim 9) to form PEG conjugated Hb protein. Winslow et al. teach the process of claim 8.

In the above method, the ratio of Hb (i.e., SFH: stroma free hemoglobulin, see col. col. 2, lines 58-59) to iminothiolane is 1:10 (Example 2, col. 16, lines 15-17), which anticipates claims 9-10 and 13-16.

In the above method, the thiolated Hb is subjected to the PEGylation by reacting with 20-fold excess of Mal-PEG (Example 2, col. 16, lines 19-21), which anticipates claims 11-16.

Since Winslow et al. teach the PEG of molecular weight (MW) 5,000 daltons, the above method anticipates claims 17-18.

For the same reason discussed above, the non-hypertensive is an inherent property of the produced PEGylated Hb, Winslow et al. anticipate claims 19-21.

The above Winslow et al. teachings with regard to the modified (PEGylated) Hb anticipates claims 22-27.

• Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Acharya et al. (US Pat. No.6017943).

In Example 9, Acharya et al. teach a PEGylated Hb produced by modification of Hb comprising (i) reacting Hb with thiolating agent, iminothiolane (col. 7, lines 64-67), and (ii) reacting the thiolated Hb with the compound having formula (Id) (col. 8, lines 1-2); this compound has the same structure as the compound (Ib) shown on columns 3-4 wherein said compound is Mal-PEG 5000 (when *n* of the formula is 125 and "Mal" refers

to malemimidyl group, see col. 4, lines 1-2). Since malemimidyl group selectively react with thiol groups and since tetramer Hb has four Cys-93(β) residues, at least two PEG chains are linked to Cys-93(β) residues. In Example 9, Acharya et al. teach that the PEGylated Hb has molecular weight (MW) about 128 Kd (col. 11, lines 52-53). Considering that each subunit of tetrameric Hb ($\alpha_2\beta_2$) has MW: 17 Kd (see "*Discussion of art*"); then the entire Hb has MW 17×4 =68 Kd. Thus, the PEGylated Hb contains about 12 PEG chains (calculation: (128 Kd-68Kd)/5 Kd =12, wherein "5 Kd is MW of monomeric PEG 5000). Thus, the PEGylated Hb taught by Acharya et al. meets all the structural limitation of instant claims; and therefore, Acharya et al. teach the product of claims 1-3.

Acharya et al. teach that use of succinimido functional group (col. 7, lines 38-40) to link the thiolated Hb with the compound of formula (Id), i.e., functionized PEG polymer, which anticipates claims 4-6.

Since the non-hypertensive is an inherent property of the PEGylated Hb (see the above discussion), the above Acharya et al. teachings anticipate claim 7.

• Claims 1-7 are rejected under 35 U.S.C. 102(e) as being anticipated by Acharya et al. (US Pat. No. 7144989 B2).

In "Experimental details" section, col. 7, left col., Acharya et al. teach a PEGylated bovine Hb containing 10 copies of PEG-5000 chains *per* Hb tetramer (col. 7, lines 47-49). The PEGylated product is generated by the thiolation of the ε-amino group of lysine of Hb via reacting Hb with iminothiolane, wherein the thiolation introduces

highly reactive and selective thiol groups for maleimide reaction (col. 7, lines 34-40). Since tetramer Hb has four Cys-93(β) residues, at least two PEG chains are linked to Cys-93(β) residues, and since thiol groups highly reactive toward hexa-succinimido group of functionized PEG (col. 7, lines 49-50), at least two out of four thiol groups of Cys-93(β) must react with succinimo group thereby be linked to PEG chain. Acharya et al. teach the product of claims 1-3.

At col. 10, lines 60-64, Acharya et al. teach attaching a succinimidyl PEG to the thiolated Hb to produce said PEGylated Hb, which anticipates claims 4-6.

Since the non-hypertensive is an inherent property of the PEGylated Hb (see the above discussion), the above Acharya et al. teachings anticipate claim 7.

Conclusion

No claims are allowed.

Discussion of art

The prior art made of record and not currently relied upon in any rejections is considered pertinent to Applicants' disclosure:

• Examiner note that claims 1-3 of US Pat. No. 7144898B2 (**989**) discloses a PEGylated hemoglobulin comprising a thiocarbamoyl-pheyl-carbamate of PEG; this PEGylation is not considered to have same chemical mechanism of thiolation mediated maleimide chemistry based PEGylation (see col. 23, lines 12-17). Therefore, the claims of 989 are not the obvious variation of the instant claims, i.e., 989 is not a reference for the double patenting issue. For the similar reasons stated above, US Pat. No. 7019117 is not a double patenting reference.

• Examiner note that claim 30 and dependent claims thereto of Application No. 10198732 (732) disclose PEG conjugated hemoglobulin wherein PEG is linked to alpha amino of Val 1 residue but not ε-amino group of Lys. Thus, the claims of 732 are not obvious variation over the instant claims. Therefore, 732 is not a double patenting reference.

• Acharya et al. (US Pat. No. 6017943) teach a process of modification of Hb comprising (i) reacting Hb with thiolating agent, iminothiolane (col. 7, lines 64-67), and (ii) reacting the thiolated Hb with the compound having formula (Id) (col. 8, lines 1-2); this compound has the same structure as the compound (Ib) shown on columns 3-4 wherein, when n is 125, said compound is Mal-PEG 5000 wherein "Mal" refers to malemimidyl functional group (col. 4, lines 1-2). In step (i), thiolating agent is about 5 to 30 fold molar excess over Hb; and in step (ii), the compound (e.g., Mal-PEG 5000) reacts with the thiolated Hb in 2-fold molar excess. Because the fold of excess in steps (i) and (ii) does not meet the limitation of claim 8 with regard to the fold of iminothiolane in step (a) and the fold of PEG having maleimidyl functional group in step (b), Acharya et al. patent is not a prior art for the claimed process of claims 8-21.

•Wikipedia ("Hemoglobulin" (2007, updated) http://en.wikipedia.org/wiki /Hemoglobin, pages 1-2) teach that each subunit of tetrameric Hb ($\alpha_2\beta_2$) has MW: 17 Kd (page 2, 4th paragraph).

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

Samuel Wei Liu, Ph.D.
Patent Examiner, Art Unit 1656
July 15, 2007

Karen Cochrane Carlson, PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER